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Items Driving WOMAC Pain Subscore Changes Due to Lorecivivint, a Potential Disease-Modifying Treatment for Knee Osteoarthritis: A Post Hoc Analysis of Phase 2b Trial Data

Sarah Kennedy, PhD, Christopher J. Swearingen, PhD, Ismail Simsek, MD, Jeyanesh Tambiah, MD

Samumed, LLC, San Diego, CA

Background: Knee osteoarthritis (OA) is a disease characterized by pain, loss of function, and structural deformities, leading to a heterogeneous disease state that can confound patient-reported outcomes (PROs). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscore addresses this reporting variability by capturing multiple pain items related to "active" and "static" subject states. We hypothesize that measurement of these "active" versus "static" pain items may demonstrate differential effect sizes when assessing treatment benefit. Lorecivivint (LOR; SM04690), a small-molecule, intra-articular CLK/DYRK1A inhibitor that modulates the Wnt pathway, is currently in development as a potential disease-modifying treatment for knee OA.[1,2]

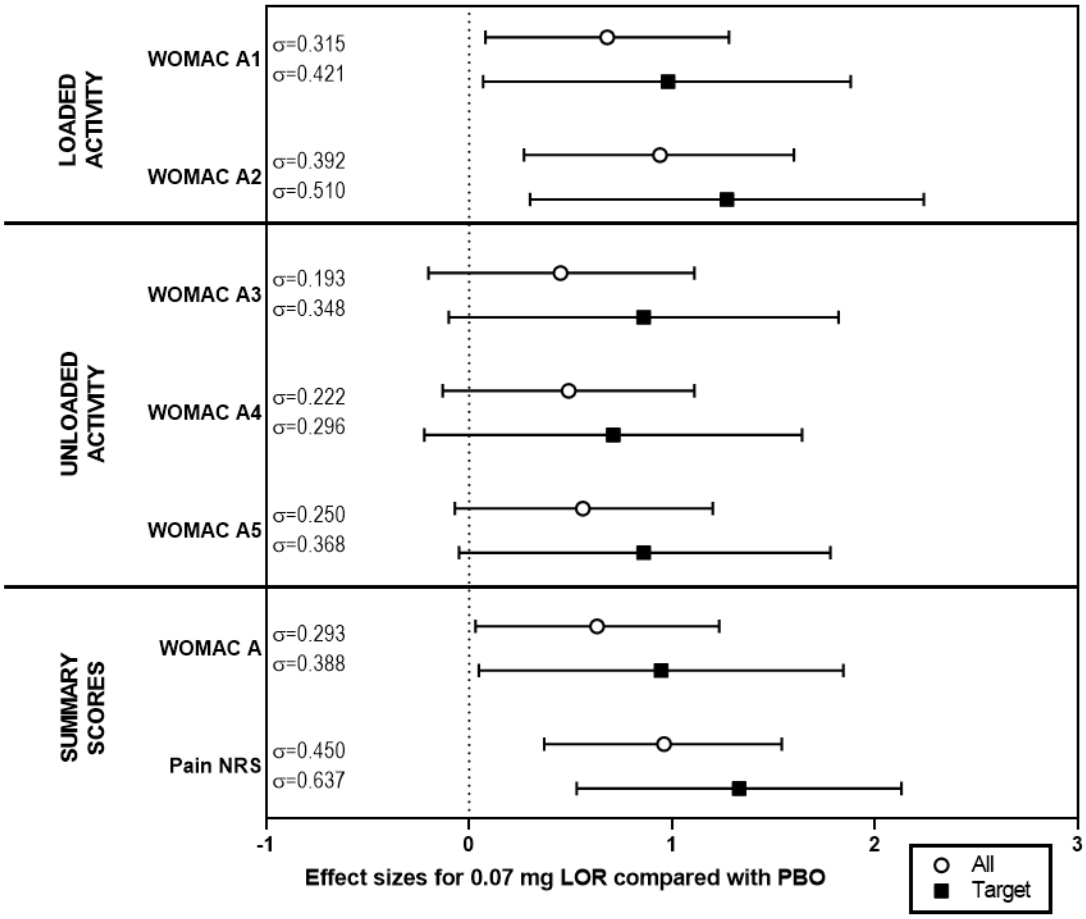
Objectives: To test the hypothesis, a post hoc analysis of Pain NRS, WOMAC Pain subscore, and individual WOMAC PROs (items A1–A5) from a Phase 2b LOR trial was performed to examine effect size (ES) changes.

Methods: The original 24-week Phase 2b trial has been previously reported. In this study, pain was assessed using the weekly average of daily Pain NRS and WOMAC Pain subscore. In the post hoc analysis, items A1–A5 (pain walking on a flat surface? [A1], going up/downstairs? [A2], at night in bed? [A3], sitting or lying down? [A4], and while standing? [A5]) were individually analyzed for subjects treated with 0.07 mg LOR and compared with the primary study outcomes of mean Pain NRS and summed mean WOMAC Pain subscore at Week 12. Baseline-adjusted analysis of covariance for WOMAC A1–A5 scores was conducted on LOR-treated subjects compared with placebo (PBO) in 1) the Full Analysis Set (FAS) of all dosed subjects and 2) a target population of subjects with fixed baseline joint space width (JSW) [2–4] mm without widespread pain (Widespread Pain Index [WPI] ≤4, Symptom Severity Score Question 2≤2).

Results: In this analysis, 231 subjects (KL grade 3 63.2%) were included. The primary study analysis demonstrated efficacy of LOR compared with PBO for Pain NRS and WOMAC Pain, with respective effect sizes of 0.450 and 0.293 (Figure). In the target population, Pain NRS and WOMAC A effect sizes increased (0.637 and 0.410, respectively). Each WOMAC A item showed less of an effect size than Pain NRS at Week 12. Treatment with 0.07 mg LOR compared with PBO showed significant improvements in effect sizes of WOMAC A1 (FAS: ES=0.315, *P*=0.028; target population: ES=0.421, *P*=0.035) and A2 (FAS: ES=0.392, *P*=0.006; target population: ES=0.510, *P*=0.011). A3–A5 did not show statistical improvement for LOR compared with PBO.

Conclusions: In the post hoc analysis, Pain NRS exhibited the greatest effect size of tested PROs after treatment with 0.07 mg LOR compared with PBO. These effect sizes were enhanced in the target population with fixed baseline JSW without widespread pain for all scores compared with the FAS. WOMAC "active" questions demonstrated greater effect sizes with LOR treatment than "static" questions and the full WOMAC Pain domain, providing support for the hypothesized dimensional constructs in knee OA pain assessment.

Figure: Effect sizes for 0.07 mg LOR compared with PBO for the FAS and target population at Week 12.



References:

1. Deshmukh V, et al. *Osteoarthritis Cartilage*. 2017.
2. Deshmukh V, et al. *Osteoarthritis Cartilage*. 2019.